Phthalonimides (1,3,4-Trioxo-1,2,3,4-tetrahydroisoquinolines) of Potential Biological Interest

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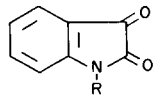
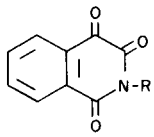
A new simple method for the preparation of phthalonimides (1,3,4-trioxo-1,2,3,4-tetrahydroisoquinolines), consisting of the selenium dioxide-oxidation of the appropriate homophthalimides, has been devised; the thiosemicarbazones and other derivatives of phthalonimides of possible biological interest (as potential antibacterial, antiviral, or immunosuppressive agents) have been synthesized.

Phthalonimides, or 1,3,4-trioxo-1,2,3,4-tetrahydroisoquinolines (II), can in theory be derived from isatins (I) by the insertion of a third carbonyl group between the imide function and the benzene ring. As several types of derivatives of isatins, such as the β-thiosemicarbazones (1), the β-thiazolinylhydrazones (2), and the *N*-Mannich bases (3), are biologically active as antiviral agents, it was deemed interesting to investigate compounds with similar molecular arrangements, but derived from phthalonimides.



I



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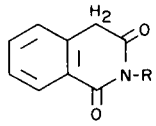


III

TABLE I

N-Substituted Homophthalimides (III)

Substituent R	Formula	M.P., °C	Analyses Calcd. C	H	N	Found C	H	N
ethyl (a)	$C_{11}H_{11}NO_2$	106	-	-	-	-	-	-
n-propyl (a)	$C_{12}H_{13}NO_2$	69	70.9	6.5	6.9	70.8	6.5	6.9
isopropyl (a)	$C_{12}H_{13}NO_2$	83	70.9	6.5	6.9	71.1	6.6	7.1
n-butyl (a)	$C_{13}H_{15}NO_2$	57	71.9	7.0	6.5	72.0	6.9	6.5
isobutyl (a)	$C_{13}H_{15}NO_2$	50	71.9	7.0	6.5	71.9	7.1	6.4
cyclohexyl (b)	$C_{15}H_{17}NO_2$	172	74.1	7.0	5.8	74.4	7.0	5.8
2,4-dimethylphenyl (b)	$C_{17}H_{15}NO_2$	178	77.0	5.7	5.3	76.9	6.0	5.5
2,5-dimethylphenyl (b)	$C_{17}H_{15}NO_2$	224	77.0	5.7	5.3	76.9	5.6	5.2

(a) Recrystallized from aqueous methanol or hexane. (b) Recrystallized from ethanol.

TABLE II

Substituted Phthalonimides (II)

Substituent R	Formula	M.P., °C	Analyses Calcd. C	H	N	Found C	H	N
ethyl (a)	$C_{11}H_9NO_3$	101	65.1	4.4	6.9	65.2	4.2	7.0
isopropyl (b)	$C_{12}H_{11}NO_3$	141	66.4	5.1	6.5	66.5	5.2	6.6
n-butyl (c)	$C_{13}H_{13}NO_3$	63	67.5	5.6	6.1	67.2	5.9	6.2
isobutyl (b)	$C_{13}H_{13}NO_3$	110	67.5	5.6	6.1	67.3	5.6	6.2
cyclohexyl (a)	$C_{15}H_{15}NO_3$	152	70.0	5.8	5.4	69.8	5.7	5.5

(a) Recrystallized from ethanol. (b) Recrystallized from methanol. (c) Recrystallized from cyclohexane.

TABLE III

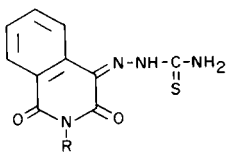
β-Thiosemicarbazones (IV) of Phthalonimides

Substituent R	Formula	M.P., °C	Analyses Calcd. C	H	N	Found C	H	N
ethyl (a)	$C_{12}H_{12}N_4O_2S$	284	52.2	4.3	20.3	52.0	4.3	20.0
n-propyl (a)	$C_{13}H_{14}N_4O_2S$	253	53.8	4.9	19.3	53.5	4.6	19.0
isopropyl (a)	$C_{13}H_{14}N_4O_2S$	312	53.8	4.9	10.3	54.1	4.8	19.0
n-butyl (b)	$C_{14}H_{16}N_4O_2S$	235	55.3	5.3	18.4	55.0	5.5	18.2
isobutyl (b)	$C_{14}H_{16}N_4O_2S$	256	55.3	5.3	18.4	55.0	5.5	18.1
cyclohexyl (a)	$C_{16}H_{18}N_4O_2S$	332	58.2	5.5	17.0	58.0	5.5	16.7

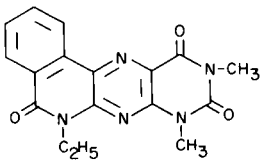
(a) Recrystallized from ethanol. (b) Recrystallized from a mixture of ethanol and benzene.

First, we looked for a simple and general route of access to the phthalonimides themselves. Hitherto these had been prepared either by oxidation of the appropriate isoquinolines with potassium permanganate (4), or, more recently (5), by bromination of homophthalimides (III), and conversion of the 4,4-dibromohomophthalimides thus obtained to the corresponding dimorpholinyl compounds which were then hydrolyzed to phthalonimides (II). This method has the advantage of the ready availability of the starting materials (homophthalimides being conveniently prepared from homophthalic acid), but it is a multi-stage, time-consuming procedure which, further, is not applicable to homophthalimides with bromine-sensitive substituents (*e.g.* *N*-alkenyl- or Bz-hydroxyhomophthalimides).

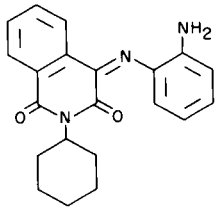
We have now found that homophthalimides can be



IV



V



VI

readily converted by selenium dioxide into the corresponding phthalonimides. Table I lists a number of homophthalimides which were used in this reaction, and Table II records the new phthalonimides thus obtained.

As trioxo compounds with only one true ketone function, phthalonimides afforded with thiosemicarbazide, monothiosemicarbazones (IV), a number of which are listed in Table III.

N-methylphthalonimide has been shown to react with *o*-phenylenediamine to give the corresponding phenazine cyclization-product (5). We now found, however, that in certain instances *N*-substituted phthalonimides react with only one amino group of the same diamine, to give the corresponding Schiff bases, *N*-cyclohexylphthalonimide, for example, affording compound VI. Interestingly, the reaction of 5,6-diamino-1,3-dimethyluracil with *N*-ethylphthalonimide readily gave the expected cyclization-product (V); in this condensation (which furnished only a single reaction-product), the amino group in position 5 of the pyrimidine ring is assumed to have reacted with the ketonic carbonyl of the phthalonimide rather than with the adjacent amide carbonyl, in view of the known superiority of the 5- over the 6-amino group in 5,6-diaminopyrimidines as concerns the formation of Schiff bases (6).

EXPERIMENTAL

Preparation of *N*-Substituted Homophthalimides (III).

Homophthalic acid (1 mole) was added in small portions to an aqueous solution of the appropriate primary amine (4 moles), and the reaction product was heated under reflux for 30-45 minutes; the solution was evaporated to dryness and the residue vacuum-distilled, to give the homophthalimide in almost theoretical yield, as silky, colorless needles.

Oxidation of Homophthalimides.

A well-stirred solution of the homophthalimide (1 mole) in anhydrous toluene was treated with finely powdered selenium dioxide (1.1 mole) and the mixture then heated under reflux for 8-12 hours. After cooling, the selenium formed was filtered off and the solvent removed from the filtrate by vacuum-distillation. The residue, consisting of the corresponding phthalonimide (obtained in *circa* 70% yield), was recrystallized from the appropriate solvent. All the phthalonimides thus prepared were pale yellow.

Preparation of the Thiosemicarbazones (IV).

A solution of the appropriate phthalonimide (1 mole) and thiosemicarbazide (1 mole) in ethanol was heated under reflux for 1-2 hours; the precipitate obtained on cooling was filtered, and recrystallized to give the thiosemicarbazone, silky, pale yellow needles, in 80-90% yield.

6-Ethyl-8-methyl-5,9,11-trioxo-5,6,8,9,10,11-hexahydroisoquino-[4,3-*g*]pteridine (V).

A solution of 2.5 g. of *N*-ethylphthalonimide and 2 g. of 5,6-diamino-1,3-dimethyluracil (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine) in 100 ml. of 1-propanol was heated under reflux for 4 hours and then concentrated; after cooling the precipitate formed was filtered off and recrystallized from dioxane, to give compound V as straw-colored prisms, m.p. 306° (yield, 80%). No isomeric product could be isolated in this preparation.

Anal. Calcd. for $C_{17}H_{15}N_5O_3$: C, 60.5; H, 4.5; N, 20.8. Found: C, 60.3; H, 4.6; N, 20.6

1-Oxo-2-ethyl-4-(*o*-aminophenylimino)-1,2,3,4-tetrahydroisoquinoline (VI).

A solution of *N*-cyclohexylphthalonimide (1 mole) and *o*-phenylenediamine (1 mole) in 1-propanol was treated as above; the reaction-product crystallized from methanol in cream colored prisms, m.p. 201° (yield, 70%).

Anal. Calcd. for $C_{21}H_{21}N_3O_2$: C, 72.6; H, 6.1; N, 12.1. Found: C, 72.9; H, 6.0; N, 11.8.

The results of determinations of antiviral and other biological activities of the substances prepared will be reported at a later date.

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Received July 8, 1968 45-Orléans-La Source, France